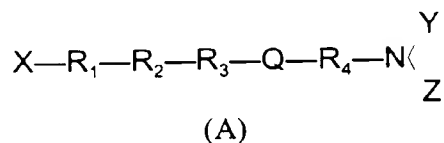


**What is claimed is:**

1. A compound of having the chemical structure of formula (A):



with peripheral analgesic effect, wherein:

- a) X is selected from the group consisting of H and C<sub>1-6</sub> alkyl;
- b) Y and Z are independently selected from the group consisting of H, cyclic aralkyl, and C<sub>1-6</sub> alkyl;
- c) R<sub>1</sub> is a tyrosyl residue or a 2',6'-dimethyltyrosyl residue;
- d) R<sub>2</sub> is an amino acid having the R-configuration, aminoisobutyric acid, cyclopropylalanine, cyclohomoleucine or cycloleucine;
- e) R<sub>3</sub> is an aromatic amino acid;
- f) R<sub>4</sub> is an aromatic amino acid residue;
- g) Q is an amide bond or an interposed amide bond mimetic;
- h) with the proviso that when:
- i) R<sub>1</sub> is a tyrosyl residue;
- ii) R<sub>2</sub> is D-alanine;
- iii) X, Y, and Z are H; and
- iv) R<sub>3</sub> is phenylalanine;
- then R<sub>4</sub> is not unsubstituted phenylalanine or phenylalanine substituted with 4NO<sub>2</sub> or 4N<sub>3</sub>;
- i) with the further proviso that when:
- i) R<sub>1</sub> is a tyrosyl residue;
- ii) R<sub>2</sub> is D-alanine;
- iii) X, Y, and Z are H; and

4NO<sub>2</sub>;

j) with the further proviso that when:

- i)  $R_1$  is a tyrosyl residue;
  - ii)  $R_2$  is D-alanine;
  - iii) X, Y, and Z are H; and
  - iv)  $R_4$  is 1'-naphthylalanine;
- then  $R_3$  is not 1'-naphthylalanine or 2'-naphthylalanine;

k) with the further proviso that when:

- i)  $R_1$  is a tyrosyl residue;
  - ii)  $R_2$  is D-alanine; and
  - iii) X, Y and Z are H,
- then both  $R_3$  and  $R_4$  are not tryptophan;

l) with the further proviso that when:

- i)  $R_1$  is a tyrosyl residue;
  - ii)  $R_2$  is a D-amino acid with a lower alkyl or lower thioalkyl group as a side chain; and
  - iii)  $R_4$  is a neutral amino acid,
- then  $R_3$  is not unsubstituted phenylalanine;

m) and wherein said compound is not selected from the group consisting of:

- H-Tyr-D-Phe-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-D-NMePhe-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-D-Tic-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-Pro-Phe-Thr(Bzl)-NH<sub>2</sub>;
- H-Tyr-Pro-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-Pro-Phe-Apb-NH<sub>2</sub>;
- H-Tyr-Pro-Phe-App-NH<sub>2</sub>;
- H-Tyr-Pro-Phe-Aph-NH<sub>2</sub>; and
- H-Tyr-Pro-Apb-Phe-NH<sub>2</sub>.

wherein Apb is 2-amino-4-phenylbutanoic acid, App is 2-amino-5-phenylpentanoic

30 2. The compound of claim 1, wherein X is H.

3. The compound of either claim 1 or 2, wherein:

a)  $R_2$  is as defined in claim 1;

b) with the proviso that when:

i)  $R_1$  is a tyrosyl residue;

ii)  $R_2$  is D-alanine; and

iii) Y and Z are H;

then  $R_3$  and  $R_4$  are different and are selected from the group consisting of phenylalanine, and tryptophan.

4. The compound of either claim 1 or claim 2, wherein Q is an amide bond or an interposed amide bond mimetic of the formula  $Q_1-Q_2$ , wherein:

a)  $Q_1$  is selected from the group consisting of  $CH_2$ ,  $CHOH$ ,  $C=O$ ,  $C=S$ , and  $CH=$ ; and

b)  $Q_2$  is selected from the group consisting of  $CH_2$ ,  $NH$ ,  $S$ ,  $SO$ ,  $SO_2$ ,  $O$ , and  $CH=$ ;

c) with the proviso that when  $Q_1$  is  $CH=$ , then  $Q_2$  is  $CH=$ .

5. The compound of claim 3, wherein Q is an amide bond or an interposed amide bond mimetic of the formula  $Q_1-Q_2$ , wherein:

a)  $Q_1$  is selected from the group consisting of  $CH_2$ ,  $CHOH$ ,  $C=O$ ,  $C=S$ , and  $CH=$ ; and

b)  $Q_2$  is selected from the group consisting of  $CH_2$ ,  $NH$ ,  $S$ ,  $SO$ ,  $SO_2$ ,  $O$ , and  $CH=$ ;

c) with the proviso that when  $Q_1$  is  $CH=$ , then  $Q_2$  is  $CH=$ .

6. The compound of claim 5, wherein:

a) Y and Z are H;

b)  $R_2$  is as defined in claim 1;

c) with the proviso that when:

i)  $R_1$  is a tyrosyl residue; and

ii)  $R_2$  is D-alanine;

then  $R_3$  and  $R_4$  are different and are selected from the group consisting of phenylalanine and tryptophan.

5 7. The compound of either claim 1 or claim 2, wherein:

a) Y and Z are H;

b)  $R_2$  is as defined in claim 1;

c)  $R_3$  is an aromatic amino acid; and

d)  $R_4$  is an aromatic amino acid;

10 e) with the proviso that when:

i)  $R_1$  is a tyrosyl residue; and

ii)  $R_2$  is D-alanine;

then  $R_3$  and  $R_4$  are different and are selected from the group consisting of phenylalanine and tryptophan.

15 8. The compound of claim 4, wherein:

a) Y and Z are H;

b)  $R_2$  is as defined in claim 1;

c)  $R_3$  is an aromatic amino acid; and

d)  $R_4$  is an aromatic amino acid;

20 e) with the proviso that when:

i)  $R_1$  is a tyrosyl residue; and

ii)  $R_2$  is D-alanine;

then  $R_3$  and  $R_4$  are different and are selected from the group consisting of phenylalanine and tryptophan.

25 9. The compound of claim 6, wherein:

a)  $R_1$  is a phenylalanyl residue; and

c)  $R_4$  is a phenylalanyl residue.

10. The compound of claim 7, wherein:
- $R_2$  is as defined in claim 1, with the proviso that  $R_2$  is not D-alanine;
  - $R_3$  is a phenylalanyl residue; and
  - $R_4$  is a phenylalanyl residue.
- 5 11. The compound of claim 8, wherein:
- $R_2$  is as defined in claim 1, with the proviso that  $R_2$  is not D-alanine;
  - $R_3$  is a phenylalanyl residue; and
  - $R_4$  is a phenylalanyl residue.
12. The compound of claim 6, wherein:
- 10
- $R_1$  is a tyrosyl residue;
  - $R_2$  is selected from the group consisting of D-serine and D-arginine;
  - $R_3$  is a phenylalanyl residue;
  - $R_4$  is a phenylalanyl residue; and
  - Q is an amide bond.
- 15 13. The compound of claim 7, wherein:
- $R_1$  is a tyrosyl residue;
  - $R_2$  is selected from the group consisting of D-serine and D-arginine;
  - $R_3$  is a phenylalanyl residue;
  - $R_4$  is a phenylalanyl residue; and
  - 20 e) Q is an amide bond.
14. The compound of claim 8, wherein:
- $R_1$  is a tyrosyl residue;
  - $R_2$  is selected from the group consisting of D-serine and D-arginine;
  - $R_3$  is a phenylalanyl residue;

15. A compound selected from the group consisting of:
- H-Tyr-Aib-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-D-Nle-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-D-Ala-Phe-2'-Nal-NH<sub>2</sub>;
- 5 H-Tyr-D-Ala-D-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-D-Ala-Phe(4NO<sub>2</sub>)-Phe(4NO<sub>2</sub>)-NH<sub>2</sub>;
- H-Tyr-D-Ala-Phe-Tic-NH<sub>2</sub>;
- H-Tyr-D-Ala-Phe-Phe(NMe)-NH<sub>2</sub>;
- H-Tyr-D-Ala-Phe-1'-Nal-NH<sub>2</sub>;
- 10 H-Tyr-D-Ala-Trp-Phe-NH<sub>2</sub>;
- H-Tyr-D-Ala-Phe-Trp-NH<sub>2</sub>;
- H-Tyr-∇Ala-Phe-Phe-NH<sub>2</sub>;
- ∇CH<sub>3</sub>-Tyr-D-Ala-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-D-Nle-Phe-Trp-NH<sub>2</sub>;
- 15 H-Tyr-D-Nle-Phe-2'-Nal-NH<sub>2</sub>;
- H-Tyr-D-Nle-Trp-Phe-NH<sub>2</sub>;
- H-Tyr-D-Ala-Trp-2'-Nal-NH<sub>2</sub>;
- H-Tyr-D-Nle-Trp-2'-Nal-NH<sub>2</sub>;
- H-Tyr-D-Nle-Trp-Trp-NH<sub>2</sub>;
- 20 H-Tyr-D-Nva-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-D-Ser-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-D-Val-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-D-Leu-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-D-Ile-Phe-Phe-NH<sub>2</sub>;
- 25 H-Tyr-D-Abu-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-Chl-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-Cle-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-D-Arg-Phe-Phe-NH<sub>2</sub>;
- H-DMI-D-Ser-Phe-Phe-NH<sub>2</sub>.

- H-Tyr-D-Ala-Phe-Phe-OH trifluoroacetate;  
 H-Tyr-D-Ala-Phe-Phg-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Phe-Hph-NH<sub>2</sub> bis-trifluoroacetic acid;  
 H-DMT-D-Ala-Phe-Phe-NH<sub>2</sub> trifluoroacetic acid;  
 5 H-D-DMT-D-Ala-Phe-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Ala-Phe-Hph-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Ala-Phe-Cys(Bzl)-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Hph-Phe-NH<sub>2</sub> bis-trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Phg-Phe-NH<sub>2</sub> bis-trifluoro acetic acid salt;  
 10 H-Tyr-D-Ala-Phe-Phe-CH<sub>2</sub>OH hydrochloride salt;  
 H-Tyr-D-Ala-Hph-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Met-Phe-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Phe-D-Phe-NH<sub>2</sub> bis-trifluoroacetic acid salt;  
 H-Tyr-D-Ala-Phg-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 15 H-Tyr-(D)-Ala-(D)-Phg-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Phe-Phe(pF)-NH<sub>2</sub> bis-trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Phe-D-Phe(pF)-NH<sub>2</sub> ditrifluoroacetic acid salt;  
 H-Tyr-D-Ala-Phe-Phe(pF)-NH<sub>2</sub> trifluoroacetic acid salt; and  
 H-Tyr-D-Ala-Phe-D-Phe(pF)-NH<sub>2</sub> trifluoroacetic acid salt.
- 20 16. The compound of claim 1, wherein said compound is H-Tyr-D-Ser-Phe-Phe-NH<sub>2</sub>.
17. The compound of claim 1, wherein said compound is H-Tyr-D-Arg-Phe-Phe-NH<sub>2</sub>.
18. A pharmaceutical composition possessing analgesic activity, comprising, in admixture with a pharmaceutically acceptable carrier, an effective amount of at least one compound having the chemical structure of formula (A):

with peripheral analgesic effect, wherein:

- a) X is selected from the group consisting of H and C<sub>1-6</sub> alkyl;
- b) Y and Z are independently selected from the group consisting of H, cyclic aralkyl, and C<sub>1-6</sub> alkyl;
- 5 c) R<sub>1</sub> is a tyrosyl residue or a 2',6'-dimethyltyrosyl residue;
- d) R<sub>2</sub> is an amino acid having the R-configuration, aminoisobutyric acid, cyclopropylalanine, cyclohomoleucine or cycloleucine;
- e) R<sub>3</sub> is an aromatic amino acid;
- f) R<sub>4</sub> is an aromatic amino acid residue;
- 10 g) Q is an amide bond or an interposed amide bond mimetic;
- h) with the proviso that when:
  - i) R<sub>1</sub> is a tyrosyl residue;
  - ii) R<sub>2</sub> is D-alanine;
  - iii) X, Y, and Z are H; and
  - 15 iv) R<sub>3</sub> is phenylalanine;
 then R<sub>4</sub> is not unsubstituted phenylalanine or phenylalanine substituted with 4NO<sub>2</sub> or 4N<sub>3</sub>;
- i) with the further proviso that when:
  - i) R<sub>1</sub> is a tyrosyl residue;
  - 20 ii) R<sub>2</sub> is D-alanine;
  - iii) X, Y, and Z are H; and
  - iv) R<sub>4</sub> is phenylalanine;
 then R<sub>3</sub> is not unsubstituted phenylalanine or phenylalanine substituted with 4NO<sub>2</sub>;
- 25 j) with the further proviso that when:
  - i) R<sub>1</sub> is a tyrosyl residue;
  - ii) R<sub>2</sub> is D-alanine;
  - iii) X, Y, and Z are H; and



k) with the further proviso that when:

- i)  $R_1$  is a tyrosyl residue;
- ii)  $R_2$  is D-alanine; and
- iii) X, Y and Z are H,

5 then both  $R_3$  and  $R_4$  are not tryptophan;

l) with the further proviso that when:

- i)  $R_1$  is a tyrosyl residue;
- ii)  $R_2$  is a D-amino acid with a lower alkyl or lower thioalkyl group as a side chain; and
- iii)  $R_4$  is a neutral amino acid,

10 then  $R_3$  is not unsubstituted phenylalanine;

m) and wherein said compound is not selected from the group consisting of:

- H-Tyr-D-Phe-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-D-NMePhe-Phe-Phe-NH<sub>2</sub>;
- 15 H-Tyr-D-Tic-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-Pro-Phe-Thr(Bz1)-NH<sub>2</sub>;
- H-Tyr-Pro-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-Pro-Phe-Apb-NH<sub>2</sub>;
- H-Tyr-Pro-Phe-App-NH<sub>2</sub>;
- 20 H-Tyr-Pro-Phe-Aph-NH<sub>2</sub>; and
- H-Tyr-Pro-Apb-Phe-NH<sub>2</sub>.

wherein Apb is 2-amino-4-phenylbutanoic acid, App is 2-amino-5-phenylpentanoic acid and Aph is 2-amino-6-phenylhexanoic acid.

19. The pharmaceutical composition of claim 18 wherein said composition has peripheral  
25 analgesic activity and wherein said compound has a chemical structure in which X is H.

20. The pharmaceutical composition of either claim 18 or claim 19 wherein said composition

a)  $R_2$  is as defined in claim 18:

- b) with the proviso that when:
- i)  $R_1$  is a tyrosyl residue;
  - ii)  $R_2$  is D-alanine; and
  - iii) Y and Z are H;

5 then  $R_3$  and  $R_4$  are different and are selected from the group consisting of phenylalanine, and tryptophan.

21. The pharmaceutical composition of either claim 18 or claim 19 wherein said composition has peripheral analgesic activity and wherein said compound has a chemical structure in which: Q is an amide bond or an interposed amide bond mimetic of the formula  $Q_1-Q_2$ ,  
10 wherein:

- a)  $Q_1$  is selected from the group consisting of  $CH_2$ ,  $CHOH$ ,  $C=O$ ,  $C=S$ , and  $CH=$ ; and
- b)  $Q_2$  is selected from the group consisting of  $CH_2$ ,  $NH$ ,  $S$ ,  $SO$ ,  $SO_2$ ,  $O$ , and  $CH=$ ;
- 15 c) with the proviso that when  $Q_1$  is  $CH=$ , then  $Q_2$  is  $CH=$ .

22. The pharmaceutical composition of 20 wherein said composition has peripheral analgesic activity and wherein said compound has a chemical structure in which: Q is an amide bond or an interposed amide bond mimetic of the formula  $Q_1-Q_2$ , wherein:

- a)  $Q_1$  is selected from the group consisting of  $CH_2$ ,  $CHOH$ ,  $C=O$ ,  $C=S$ , and  $CH=$ ; and
- 20 b)  $Q_2$  is selected from the group consisting of  $CH_2$ ,  $NH$ ,  $S$ ,  $SO$ ,  $SO_2$ ,  $O$ , and  $CH=$ ;
- c) with the proviso that when  $Q_1$  is  $CH=$ , then  $Q_2$  is  $CH=$ .

23. The pharmaceutical composition of claim 22, wherein said composition has peripheral  
25 analgesic activity and wherein said compound has a chemical structure in which:

- was defined in claim 11.
- c)  $R_1$  is an aromatic amino acid; and

- d)  $R_4$  is an aromatic amino acid;
- e) with the proviso that when:
  - i)  $R_1$  is a tyrosyl residue; and
  - ii)  $R_2$  is D-alanine;

5 then  $R_3$  and  $R_4$  are different and are selected from the group consisting of phenylalanine and tryptophan.

24. The pharmaceutical composition of either claim 18 or 19, wherein said composition has peripheral analgesic activity and wherein said compound has a chemical structure in which:

- a) Y and Z are H;
- 10 b)  $R_2$  is as defined in claim 18;
- c)  $R_3$  is an aromatic amino acid; and
- d)  $R_4$  is an aromatic amino acid;
- e) with the proviso that when:
  - i)  $R_1$  is a tyrosyl residue; and
  - 15 ii)  $R_2$  is D-alanine;

then  $R_3$  and  $R_4$  are different and are selected from the group consisting of phenylalanine and tryptophan.

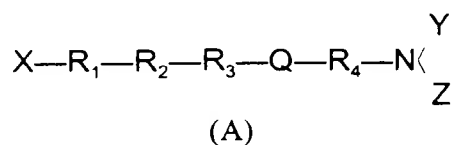
25. The pharmaceutical composition of claim 18, further comprising an effective amount of at least one other therapeutically active agent.

20 26. The pharmaceutical composition of claim 20, further comprising an effective amount of at least one other therapeutically active agent.

27. The pharmaceutical composition of claim 21, further comprising an effective amount of at least one other therapeutically active agent.

28. The pharmaceutical composition of claim 22, further comprising an effective amount of at least one other therapeutically active agent.

29. The pharmaceutical composition of claim 24, further comprising an effective amount of at least one other therapeutically active agent.
30. A method for the treatment of pain comprising the step of administering to a mammal in need of such treatment a pharmaceutically effective amount of at least one compound having the chemical structure of formula (A):



10 wherein:

- a) X is selected from the group consisting of H and C<sub>1-6</sub> alkyl;
- b) Y and Z are independently selected from the group consisting of H, cyclic aralkyl, and C<sub>1-6</sub> alkyl;
- c) R<sub>1</sub> is a tyrosyl residue or a 2',6'-dimethyltyrosyl residue;
- 15 d) R<sub>2</sub> is an amino acid having the R-configuration, aminoisobutyric acid, cyclopropylalanine, cyclohomoleucine or cycloleucine;
- e) R<sub>3</sub> is an aromatic amino acid;
- f) R<sub>4</sub> is an aromatic amino acid residue;
- g) Q is an amide bond or an interposed amide bond mimetic;
- 20 h) with the proviso that when:
- i) R<sub>1</sub> is a tyrosyl residue;
- ii) R<sub>2</sub> is D-alanine;
- iii) X, Y, and Z are H; and
- iv) R<sub>3</sub> is phenylalanine;
- 25 then R<sub>4</sub> is not unsubstituted phenylalanine or phenylalanine substituted with 4NO<sub>2</sub> or 4N<sub>3</sub>;

- ii) R<sub>2</sub> is D-alanine;

iii) X, Y, and Z are H; and

iv) R<sub>4</sub> is phenylalanine;

then R<sub>3</sub> is not unsubstituted phenylalanine or phenylalanine substituted with 4NO<sub>2</sub>;

5 j) with the further proviso that when:

i) R<sub>1</sub> is a tyrosyl residue;

ii) R<sub>2</sub> is D-alanine;

iii) X, Y, and Z are H; and

iv) R<sub>4</sub> is 1'-naphthylalanine;

10 then R<sub>3</sub> is not 1'-naphthylalanine or 2'-naphthylalanine;

k) with the further proviso that when:

i) R<sub>1</sub> is a tyrosyl residue;

ii) R<sub>2</sub> is D-alanine; and

iii) X, Y and Z are H,

15 then both R<sub>3</sub> and R<sub>4</sub> are not tryptophan;

l) with the further proviso that when:

i) R<sub>1</sub> is a tyrosyl residue;

ii) R<sub>2</sub> is a D-amino acid with a lower alkyl or lower thioalkyl group as a side chain; and

20 iii) R<sub>4</sub> is a neutral amino acid,

then R<sub>3</sub> is not unsubstituted phenylalanine;

m) and wherein said compound is not selected from the group consisting of:

H-Tyr-D-Phe-Phe-Phe-NH<sub>2</sub>;

H-Tyr-D-NMePhe-Phe-Phe-NH<sub>2</sub>;

25 H-Tyr-D-Tic-Phe-Phe-NH<sub>2</sub>;

H-Tyr-Pro-Phe-Thr(Bz1)-NH<sub>2</sub>;

H-Tyr-Pro-Phe-Phe-NH<sub>2</sub>;

H-Tyr-Pro-Phe-Apb-NH<sub>2</sub>;

H-Tyr-Pro-Phe-NH<sub>2</sub>;

H-Tyr-Pro-Apb-Phe-NH<sub>2</sub>

wherein Apb is 2-amino-4-phenylbutanoic acid, App is 2-amino-5-phenylpentanoic acid and Aph is 2-amino-6-phenylhexanoic acid.

31. The method of claim 30, wherein said compound has a chemical structure in which X is H.

32. The method of either claim 30 or claim 31, wherein said compound has a chemical structure in which:

- a)  $R_2$  is as defined in claim 30;
- b) with the proviso that when:
  - i)  $R_1$  is a tyrosyl residue;
  - ii)  $R_2$  is D-alanine; and
  - iii) Y and Z are H;

then  $R_3$  and  $R_4$  are different and are selected from the group consisting of phenylalanine, and tryptophan.

33. The method of either claim 30 or claim 31, wherein said compound has a chemical structure in which: Q is an amide bond or an interposed amide bond mimetic of the formula  $Q_1-Q_2$ , wherein:

- a)  $Q_1$  is selected from the group consisting of  $CH_2$ ,  $CHOH$ ,  $C=O$ ,  $C=S$ , and  $CH=$ ; and
- b)  $Q_2$  is selected from the group consisting of  $CH_2$ ,  $NH$ ,  $S$ ,  $SO$ ,  $SO_2$ ,  $O$ , and  $CH=$ ;
- c) with the proviso that when  $Q_1$  is  $CH=$ , then  $Q_2$  is  $CH=$ .

34. The method of claim 32, wherein said compound has a chemical structure in which: Q is an amide bond or an interposed amide bond mimetic of the formula  $Q_1-Q_2$ , wherein:

- a)  $Q_1$  is selected from the group consisting of  $CH_2$ ,  $CHOH$ ,  $C=O$ ,  $C=S$ , and  $CH=$ ; and
- c) with the proviso that when  $Q_1$  is  $CH=$ , then  $Q_2$  is  $CH-$ .

35. The method of 34, wherein said compound has a chemical structure in which:

- a) Y and Z are H;
- b)  $R_2$  is as defined in claim 30;
- c)  $R_3$  is an aromatic amino acid; and
- d)  $R_4$  is an aromatic amino acid;
- e) with the proviso that when:

- i)  $R_1$  is a tyrosyl residue; and
- ii)  $R_2$  is D-alanine;

then  $R_3$  and  $R_4$  are different and are selected from the group consisting of phenylalanine and tryptophan.

36. The method of either claim 30 or 31, wherein said compound has a chemical structure in which:

- a) Y and Z are H;
- b)  $R_2$  is as defined in claim 30;
- c)  $R_3$  is an aromatic amino acid; and
- d)  $R_4$  is an aromatic amino acid;
- e) with the proviso that when:

- i)  $R_1$  is a tyrosyl residue; and
- ii)  $R_2$  is D-alanine;

then  $R_3$  and  $R_4$  are different and are selected from the group consisting of phenylalanine and tryptophan.

37. A method for the treatment of pain comprising the step of administering to a mammal in need of such treatment a pharmaceutically effective amount of a pharmaceutical composition possessing analgesic activity, wherein said pharmaceutical composition comprises, in admixture with a pharmaceutically acceptable carrier, an effective amount of at least one compound having the chemical structure of formula (A):

(A)

wherein:

- a) X is selected from the group consisting of H and C<sub>1-6</sub> alkyl;
- b) Y and Z are independently selected from the group consisting of H, cyclic aralkyl, and C<sub>1-6</sub> alkyl;
- 5 c) R<sub>1</sub> is a tyrosyl residue or a 2',6'-dimethyltyrosyl residue;
- d) R<sub>2</sub> is an amino acid having the R-configuration, aminoisobutyric acid, cyclopropylalanine, cyclohomoleucine or cycloleucine;
- e) R<sub>3</sub> is an aromatic amino acid;
- f) R<sub>4</sub> is an aromatic amino acid residue;
- 10 g) Q is an amide bond or an interposed amide bond mimetic;
- h) with the proviso that when:
  - i) R<sub>1</sub> is a tyrosyl residue;
  - ii) R<sub>2</sub> is D-alanine;
  - iii) X, Y, and Z are H; and
  - 15 iv) R<sub>3</sub> is phenylalanine;
 then R<sub>4</sub> is not unsubstituted phenylalanine or phenylalanine substituted with 4NO<sub>2</sub> or 4N<sub>3</sub>;
- i) with the further proviso that when:
  - i) R<sub>1</sub> is a tyrosyl residue;
  - 20 ii) R<sub>2</sub> is D-alanine;
  - iii) X, Y, and Z are H; and
  - iv) R<sub>4</sub> is phenylalanine;
 then R<sub>3</sub> is not unsubstituted phenylalanine or phenylalanine substituted with 4NO<sub>2</sub>;
- 25 j) with the further proviso that when:
  - i) R<sub>1</sub> is a tyrosyl residue;
  - ii) R<sub>2</sub> is D-alanine;
  - iii) X, Y, and Z are H; and
- k) with the further proviso that when:



- i)  $R_1$  is a tyrosyl residue;
  - ii)  $R_2$  is D-alanine; and
  - iii) X, Y and Z are H,
- then both  $R_3$  and  $R_4$  are not tryptophan;

5 l) with the further proviso that when:

- i)  $R_1$  is a tyrosyl residue;
- ii)  $R_2$  is a D-amino acid with a lower alkyl or lower thioalkyl group as a side chain; and
- iii)  $R_4$  is a neutral amino acid,

10 then  $R_3$  is not unsubstituted phenylalanine;

m) and wherein said compound is not selected from the group consisting of:

- H-Tyr-D-Phe-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-D-NMePhe-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-D-Tic-Phe-Phe-NH<sub>2</sub>;
- 15 H-Tyr-Pro-Phe-Thr(Bzl)-NH<sub>2</sub>;
- H-Tyr-Pro-Phe-Phe-NH<sub>2</sub>;
- H-Tyr-Pro-Phe-Apb-NH<sub>2</sub>;
- H-Tyr-Pro-Phe-App-NH<sub>2</sub>;
- H-Tyr-Pro-Phe-Aph-NH<sub>2</sub>; and
- 20 H-Tyr-Pro-Apb-Phe-NH<sub>2</sub>.

wherein Apb is 2-amino-4-phenylbutanoic acid, App is 2-amino-5-phenylpentanoic acid and Aph is 2-amino-6-phenylhexanoic acid.

38. The method of claim 37, wherein said pharmaceutical composition has peripheral analgesic activity and wherein said compound has a chemical structure in which X is H.

25 39. The method of either claim 37 or claim 38, wherein said pharmaceutical composition has peripheral analgesic activity and wherein said compound has a chemical structure in which:

- 1)  $R_1$  is a tyrosyl residue;

- ii)  $R_2$  is D-alanine; and
- iii) Y and Z are H;

then  $R_3$  and  $R_4$  are different and are selected from the group consisting of phenylalanine, and tryptophan.

- 5 40. The method of either claim 37 or claim 38, wherein said pharmaceutical composition has peripheral analgesic activity and wherein said compound has a chemical structure in which: Q is an amide bond or an interposed amide bond mimetic of the formula  $Q_1-Q_2$ , wherein:
- a)  $Q_1$  is selected from the group consisting of  $CH_2$ ,  $CHOH$ ,  $C=O$ ,  $C=S$ , and  $CH=$ ; and
  - 10 b)  $Q_2$  is selected from the group consisting of  $CH_2$ ,  $NH$ ,  $S$ ,  $SO$ ,  $SO_2$ ,  $O$ , and  $CH=$ ;
  - c) with the proviso that when  $Q_1$  is  $CH=$ , then  $Q_2$  is  $CH=$ .
41. The method of claim 39, wherein said pharmaceutical composition has peripheral analgesic activity and wherein said compound has a chemical structure in which: Q is an amide bond or an interposed amide bond mimetic of the formula  $Q_1-Q_2$ , wherein:
- 15 a)  $Q_1$  is selected from the group consisting of  $CH_2$ ,  $CHOH$ ,  $C=O$ ,  $C=S$ , and  $CH=$ ; and
  - b)  $Q_2$  is selected from the group consisting of  $CH_2$ ,  $NH$ ,  $S$ ,  $SO$ ,  $SO_2$ ,  $O$ , and  $CH=$ ;
  - 20 c) with the proviso that when  $Q_1$  is  $CH=$ , then  $Q_2$  is  $CH=$ .
42. The method of claim 41, wherein said pharmaceutical composition has peripheral analgesic activity and wherein said compound has a chemical structure in which:
- a) Y and Z are H;
  - b)  $R_2$  is as defined in claim 37;
  - 25 c)  $R_3$  is an aromatic amino acid; and

with the proviso that, when:

- i)  $R_4$  is a tyrosyl residue; and

ii)  $R_2$  is D-alanine;  
then  $R_3$  and  $R_4$  are different and are selected from the group consisting of  
phenylalanine and tryptophan.

43. The method of either claim 37 or claim 38, wherein said pharmaceutical composition has  
5 peripheral analgesic activity and wherein said compound has a chemical structure in which:
- a) Y and Z are H;
  - b)  $R_2$  is as defined in claim 37;
  - c)  $R_3$  is an aromatic amino acid; and
  - d)  $R_4$  is an aromatic amino acid;
  - 10 e) with the proviso that when:
    - i)  $R_1$  is a tyrosyl residue; and
    - ii)  $R_2$  is D-alanine;then  $R_3$  and  $R_4$  are different and are selected from the group consisting of  
phenylalanine and tryptophan.
- 15 44. The method of claim 37, wherein said pharmaceutical composition further comprises an  
effective amount of at least one other therapeutically active agent.
45. The method of claim 39, wherein said pharmaceutical composition further comprises an  
effective amount of at least one other therapeutically active agent.
46. The method of claim 40, wherein said pharmaceutical composition further comprises an  
20 effective amount of at least one other therapeutically active agent.
47. The method of claim 42, wherein said pharmaceutical composition further comprises an  
effective amount of at least one other therapeutically active agent.

49. A method for the treatment of pain comprising the step of administering to a mammal in need of such treatment, a pharmaceutically effective amount of the compound H-Tyr-D-Ala-Phe-Phe-NH<sub>2</sub> or analogues or pharmaceutically acceptable derivatives thereof.
50. The method of claim 49, wherein said analogue is selected from the group consisting of:  
 5 H-Tyr-D-Ala-Phe-Phe(4-NO<sub>2</sub>)-NH<sub>2</sub>, and H-Tyr-D-Ala-Phe-Phe(4-NO<sub>3</sub>)-NH<sub>2</sub>.
51. A pharmaceutical composition having analgesic activity, comprising in admixture with a pharmaceutically acceptable carrier, an effective amount of at least one peptide selected from the group consisting of:
- 10 H-Tyr-Aib-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-D-Nle-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-D-Ala-Phe-2'-Nal-NH<sub>2</sub>;  
 H-Tyr-D-Ala-D-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-D-Ala-Phe(4NO<sub>2</sub>)-Phe(4NO<sub>2</sub>)-NH<sub>2</sub>;  
 H-Tyr-D-Ala-Phe-Tic-NH<sub>2</sub>;
- 15 H-Tyr-D-Ala-Phe-Phe(NMe)-NH<sub>2</sub>;  
 H-Tyr-D-Ala-Phe-1'Nal-NH<sub>2</sub>;  
 H-Tyr-D-Ala-Trp-Phe-NH<sub>2</sub>;  
 H-Tyr-D-Ala-Phe-Trp-NH<sub>2</sub>;  
 H-Tyr-∇Ala-Phe-Phe-NH<sub>2</sub>;
- 20 ∇CH<sub>2</sub>-Tyr-D-Ala-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-D-Nle-Phe-Trp-NH<sub>2</sub>;  
 H-Tyr-D-Nle-Phe-2'-Nal-NH<sub>2</sub>;  
 H-Tyr-D-Nle-Trp-Phe-NH<sub>2</sub>;  
 H-Tyr-D-Ala-Trp-2'-Nal-NH<sub>2</sub>;
- 25 H-Tyr-D-Nle-Trp-2'-Nal-NH<sub>2</sub>;  
 H-Tyr-D-Nle-Trp-Trp-NH<sub>2</sub>;
- SCHEMATICALLY
- H-Tyr-D-Val-Phe-Phe-NH<sub>2</sub>;

- H-Tyr-D-Leu-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-D-Ile-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-D-Abu-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-Chl-Phe-Phe-NH<sub>2</sub>;  
 5 H-Tyr-Cle-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-D-Arg-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-D-Cys-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-D-Thr-Phe-Phe-NH<sub>2</sub>;  
 H-DMT-D-Ser-Phe-Phe-NH<sub>2</sub>;  
 10 H-Tyr-D-Ala-Phe-Phe-OH trifluoroacetate;  
 H-Tyr-D-Ala-Phe-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Phe-Hph-NH<sub>2</sub> bis-trifluoroacetic acid;  
 H-DMT-D-Ala-Phe-Phe-NH<sub>2</sub> trifluoroacetic acid;  
 H-D-DMT-D-Ala-Phe-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 15 H-Tyr-D-Ala-Phe-Hph-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Ala-Phe-Cys(Bzl)-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Hph-Phe-NH<sub>2</sub> bis-trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Phe-Phe-NH<sub>2</sub> bis-trifluoroacetic acid salt;  
 H-Tyr-D-Ala-Phe-Phe-CH<sub>2</sub>OH hydrochloride salt;  
 20 H-Tyr-D-Ala-Hph-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Met-Phe-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Phe-D-Phe-NH<sub>2</sub> bis-trifluoroacetic acid salt;  
 H-Tyr-D-Ala-Phe-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-(D)-Ala-(D)-Phe-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 25 H-Tyr-D-Arg-Phe-Phe(pF)-NH<sub>2</sub> bis-trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Phe-D-Phe(pF)-NH<sub>2</sub> ditrifluoroacetic acid salt;  
 H-Tyr-D-Ala-Phe-Phe(pF)-NH<sub>2</sub> trifluoroacetic acid salt; and  
 H-Tyr-D-Ala-Phe-D-Phe(pF)-NH<sub>2</sub> trifluoroacetic acid salt.
- H-Tyr-D-Nva-Phe-Phe-NH<sub>2</sub>.

53. The pharmaceutical composition of claim 51, wherein said peptide is  
H-Tyr-D-Ser-Phe-Phe-NH<sub>2</sub>.

54. The pharmaceutical composition of claim 51, wherein said peptide is  
H-Tyr-D-Arg-Phe-Phe-NH<sub>2</sub>.

5

55. A method for the treatment of pain, comprising the step administering to a mammal in need of such treatment a pharmaceutically effective amount of a peptide selected from the group consisting of:

H-Tyr-Aib-Phe-Phe-NH<sub>2</sub>;

10 H-Tyr-D-Nle-Phe-Phe-NH<sub>2</sub>;

H-Tyr-D-Ala-Phe-2'-Nal-NH<sub>2</sub>;

H-Tyr-D-Ala-D-Phe-Phe-NH<sub>2</sub>;

H-Tyr-D-Ala-Phe(4NO<sub>2</sub>)-Phe(4NO<sub>2</sub>)-NH<sub>2</sub>;

H-Tyr-D-Ala-Phe-Tic-NH<sub>2</sub>;

15 H-Tyr-D-Ala-Phe-Phe(NMe)-NH<sub>2</sub>;

H-Tyr-D-Ala-Phe-1'-Nal-NH<sub>2</sub>;

H-Tyr-D-Ala-Trp-Phe-NH<sub>2</sub>;

H-Tyr-D-Ala-Phe-Trp-NH<sub>2</sub>;

H-Tyr-∇Ala-Phe-Phe-NH<sub>2</sub>;

20 ∇CH<sub>2</sub>-Tyr-D-Ala-Phe-Phe-NH<sub>2</sub>;

H-Tyr-D-Nle-Phe-Trp-NH<sub>2</sub>;

H-Tyr-D-Nle-Phe-2'-Nal-NH<sub>2</sub>;

H-Tyr-D-Nle-Trp-Phe-NH<sub>2</sub>;

H-Tyr-D-Ala-Trp-2'-Nal-NH<sub>2</sub>;

25 H-Tyr-D-Nle-Trp-2'-Nal-NH<sub>2</sub>;

H-Tyr-D-Nle-Trp-Trp-NH<sub>2</sub>;

H-Tyr-D-Nva-Phe-Phe-NH<sub>2</sub>;

30

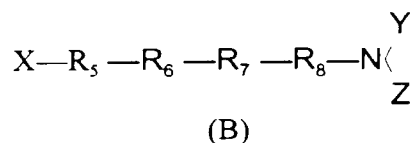
H-Tyr-D-Leu-Phe-Phe-NH<sub>2</sub>;

- H-Tyr-D-Ile-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-D-Abu-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-Chl-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-Cle-Phe-Phe-NH<sub>2</sub>;  
 5 H-Tyr-D-Arg-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-D-Cys-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-D-Thr-Phe-Phe-NH<sub>2</sub>;  
 H-DMT-D-Ser-Phe-Phe-NH<sub>2</sub>;  
 H-Tyr-D-Ala-Phe-Phe-OH trifluoroacetate;  
 10 H-Tyr-D-Ala-Phe-Phg-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Phe-Hph-NH<sub>2</sub> bis-trifluoroacetic acid;  
 H-DMT-D-Ala-Phe-Phe-NH<sub>2</sub> trifluoroacetic acid;  
 H-D-DMT-D-Ala-Phe-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Ala-Phe-Hph-NH<sub>2</sub> trifluoroacetic acid salt;  
 15 H-Tyr-D-Ala-Phe-Cys(Bzl)-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Hph-Phe-NH<sub>2</sub> bis-trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Phg-Phe-NH<sub>2</sub> bis-trifluoro acetic acid salt;  
 H-Tyr-D-Ala-Phe-Phe-CH<sub>2</sub>OH hydrochloride salt;  
 H-Tyr-D-Ala-Hph-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 20 H-Tyr-D-Met-Phe-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Phe-D-Phe-NH<sub>2</sub> bis-trifluoroacetic acid salt;  
 H-Tyr-D-Ala-Phg-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-(D)-Ala-(D)-Phg-Phe-NH<sub>2</sub> trifluoroacetic acid salt;  
 H-Tyr-D-Arg-Phe-Phe(pF)-NH<sub>2</sub> bis-trifluoroacetic acid salt;  
 25 H-Tyr-D-Arg-Phe-D-Phe(pF)-NH<sub>2</sub> ditrifluoroacetic acid salt;  
 H-Tyr-D-Ala-Phe-Phe(pF)-NH<sub>2</sub> trifluoroacetic acid salt; and  
 H-Tyr-D-Ala-Phe-D-Phe(pF)-NH<sub>2</sub> trifluoroacetic acid salt.

57. The method of claim 55, wherein said peptide is H-Tyr-D-Ser-Phe-Phe-NH<sub>2</sub>.

58. The method of claim 55, wherein said peptide is H-Tyr-D-Arg-Phe-Phe-NH<sub>2</sub>.

59. A compound of formula (B):



and salts thereof wherein,

- a) R<sub>5</sub> is Tyr or 2',6'-dimethyltyrosine, or an analog or derivative thereof;
- b) R<sub>6</sub> is D-Ala or D-Arg;
- c) R<sub>7</sub> is Phe(pF);
- d) R<sub>8</sub> is Phe or Phe(pF);
- e) X is H or C<sub>1-6</sub> alkyl; and
- f) Y and Z are independently H, aralkyl or C<sub>1-6</sub> alkyl.

60. The compound according to claim 59, wherein R<sub>6</sub> is D-Ala.

61. The compound according to claim 59, wherein R<sub>6</sub> is D-Arg.

62. The compound according to claim 59, R<sub>8</sub> is Phe.

63. The compound according to claim 62, wherein R<sub>6</sub> is D-Ala.

64. The compound according to claim 62, wherein R<sub>6</sub> is D-Arg.

65. The compound according to any one of claims 59-64 wherein X is H, and Y and Z are both H.



H-Tyr-D-Ala-Phe(pF)-Phe(pF)-NH<sub>2</sub>; and  
H-Tyr-D-Ala-Phe(pF)-Phe-NH<sub>2</sub>.

67. The compound H-Tyr-D-Ala-Phe(pF)-Phe-NH<sub>2</sub>.

68. The compound according to claim 59, wherein said compound is selected from the group  
5 consisting of:

H-Tyr-D-Arg-Phe(pF)-Phe(pF)-NH<sub>2</sub> and  
H-Tyr-D-Arg-Phe(pF)-Phe-NH<sub>2</sub>.

69. The compound H-Tyr-D-Arg-Phe(pF)-Phe-NH<sub>2</sub>,

70. A pharmaceutical composition comprising a compound according to any one of claims 59-  
10 64, or 66-69 in admixture with a pharmaceutically acceptable carrier.

71. A pharmaceutical composition comprising a compound according to claim 65, in admixture  
with a pharmaceutically acceptable carrier.

72. A method for the treatment of pain comprising, administering to a mammal in need of such  
15 treatment a pharmaceutically effective amount of a compound according to any one of  
claims 59-64 or 66-69.

73. The method of claim 72, wherein said peptides are administered to a human at a dosage of  
between 0.05 mg/kg and 20 mg/kg.

74. The method of claim 73, wherein said peptides are administered at a dosage of between 0.1  
mg/kg and 1.0 mg/kg.

76. The method of claim 75, wherein said peptides are administered to a human at a dosage of between 0.05 mg/kg and 20 mg/kg.
77. The method of claim 75, wherein said peptides are administered at a dosage of between 0.1 mg/kg and 1.0 mg/kg.